Journal of Petroleum & Environmental Biotechnology

Khan et., J Pet Environ Biotechnol 2013, 4:6
DOI: 10.4172/2157-7463.1000161

Review Article Open Access

In Silico Approach for the Bioremediation of Toxic Pollutants

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Abstract

Microbial degradation is considered as one of the environment friendly and cost-effective method for restoration of ecological niches contaminated with chemical pollutants. Thus before the application of microbial system for the degradation of any newly released pollutant in the environment, there is need to in silico study for predicting the possible degradation pathways by using various computational tools. There are large number of databases and computer programs available to perform the computational analysis for assisting the development and implementation of microbial bioremediation. The present review provides a comprehensive account of these databases, software, their respective work methodologies and potential application for the bioremediation. The information collected for the above study from different in silico resources for assisting the environmental degradation studies is discussed.

Keywords: Bioremediation; Database; Pollutant; Metabolic network; Bioinformatics

Introduction

Studies pertaining to re-establishment of polluted ecological niches have led to a generalized acceptance of microbial potential as environment friendly and cost effective measure by their decontamination of pollutant [1-5]. The enrichment of cultures have been proposed as one of the most potent approaches to restore the sites contaminated with pollutants, however, it has been considered as one of the demanding challenge for a long time uses [6,7]. Even though, isolation of culturable microbial strains is also one of the most important bottle-neck for the successful biodegradation [5]. Subsequently, other limitations (chemical complexity of the target pollutant, transformation of pollutant substrate into more toxic intermediates) are known to inhibit the speedy progress of the microbial bioremediation projects [8]. In the recent past, the microbial degradation studies have been pursued with a system biology approach, wherein the degradation studies are devised on the past experiences and information obtained with earlier studies [9-12]. This has resulted in a very strong need for the maintenance and easy access to this information. Consequently, there is a need for computational programs that can utilize all the available information regarding bioremediation. Thus use of various computational programmes, software, tools and database, a lot of things can be subjected to prediction approaches with the eventual objective of developing an applicable bioremediation technology. Conventionally, bioremediation studies have depended upon isolation of degradative microbial strain from the contaminated habitat [5,6]. Further the application of isolated strain for bioremediation in the field principally depends upon the environmental limiting factor [13]. Hence, it is necessary to implement bioremediation process in natural environmental conditions where microorganism faces the different challenges impose by various abiotic and biotic factors [14-16]. However, the efficiency of the degradation process under different mechanism affected by these factors [13]. Thus, to understand the mechanism of degradation several studies has been designed to investigate the effect of all environmental factor(s) [17,18]. To study the biodegradation from lab to field, there should be ecological sustainability of the degradative strain in the field study. Thus, before going to ex situ and in situ bioremediation of any pollutants there is need to develop in silico method for the study of degradation. The present review article describes the collection of all databases, tools and softwares which helps in the in silico analysis/prediction of toxicity of any chemical along with elucidation of feasible microbial degradation pathways.

In silico toxicity of the compounds

For environmental cleanup of the toxic compounds by microorganisms many technologies have been developed, but without the knowledge of the toxicity level of the compounds it cannot be fully successful as toxicity affects the survival of the degradative strains [19]. Thus before making many efforts in development of in silico bioremediation technology of any chemicals there is also need to predict its toxicity levels by in silico approaches. Predicting toxicity of a compound by in silico toxicological methods is a developing field with great potential. More than 70 million chemicals were identified till 29 May 2013 (CAS) [20]. Exposures of these toxic chemicals e.g., pesticides, products of chemical industries like cosmetics and drugs etc. leads to various health effects [21]. Several in silico procedures have been developed and rooted by pharmaceutical industry to understand the pharmacodynamic, pharmacokinetic and toxicological profile of a compound [22]. Tables 1 and 2 summarises various databases, methods, homology models, pharmacophores and several other molecular modelling approaches for determining the toxicity of any chemical. Although there are many data bases developed about toxicity of the compounds [23], toxicity value hierarchy from Environmental Protection Agency's (EPA), and toxicity assay method [24-26]. However, various industries are synthesizing new chemicals more rapidly than academic research and the norms lay down by the regulatory agencies. The quantitative structure-activity relationships (QSARs) are the one such in silico method for determining the quantitative structure-activity relationship model, which is based on

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Received October 07, 2013; **Accepted** November 22, 2013; **Published** November 29, 2013

Citation: Khan F, Sajid M, Cameotra SS (2013) In Silico Approach for the Bioremediation of Toxic Pollutants. J Pet Environ Biotechnol 4: 161. doi:10.4172/2157-7463.1000161

S.No	Name of Programme	URLCode	Properties/Reference
1.	Derek (Lhasa Ltd)	http://www.lhasalimited.org/	Lhasa Limited specialises in the development of *in silico* prediction and database systems for use in metabolism, toxicology and related sciences.
2.	HazardExpert (CompuDrug)	http://www.compudrug.com/	CompuDrug is software tool to estimate toxicity of an organic compound in higher animals.
3.	ACD/Tox Suite (ToxBoxes)	http://www.acdlabs.com/products/pcadmet/tox/tox/	ACD/Tox Suite is a collection of software modules that predict probabilities for basic toxicity endpoints.
4.	ADMET Predictor	http://www.simulations-plus.com/Products.aspx?pID=13	ADMET acronym indicates all the parameters associated with absorption, metabolism, distribution, elimination, and toxicity of chemical in the human tissue.
5.	OncoLogic (USEPA)	http://www.epa.gov/oppt/sf/pubs/oncologic.htm	OncoLogic™ is a computer program that evaluates the likelihood that a chemical may cause cancer.
6.	Toxtree (JRC)	http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/toxtree	Toxtree open-source application that classifies toxic chemicals into various categories and predicts their toxic effect by using decision tree approaches.
7.	MolCode Toolbox	http://www.molcode.com	Molcode Toolboxe applies to simulate various experimentally unknown properties of compounds including physical, chemical, biological, ADME-Tox, ecological pathways/ eco-toxicity and adverse drug effects.
8.	TerraQSAR™	http://www.terrabase-inc.com/	TerraQSAR™ computation programs are designed for the quick and reliable estimation of biological effects and physico-chemical properties of organic compounds.
9.	Toxicity Estimation software tool (T.E.S.T)	http://www.epa.gov/nrmrl/std/qsar/qsar.html	TEST will enable users to easily estimate acute toxicity using several different QSAR methodologies including a hierarchical method, FDA method, Single-model method, Group contribution method, Nearest neighbour method, **Random forest method, multiple linear regressions, and Consensus method.**
10.	ORCHESTRA	http://www.orchestra-qsar.eu	A project funded by EC to disseminate recent research on computer-based methods to evaluate the toxicity of hazardous chemicals [64].
11.	VirtualToxLa	http://www.biograf.ch	It is an *in silico* tool for predicting the toxicity of drugs, chemicals, and natural products. It simulates and quantifies their relations toward a series of proteins known to trigger adverse effects using automated, flexible docking combined with multidimensional QSAR [65].

Table 1: Software tools for toxicity prediction.

S.No.	Name of Database	URLCode	Properties/Reference
1.	Acutoxbase	https://acubase.amwaw.edu.pl	Acutebase has been developed to manage all information relevant to the EU integrated project 'ACuteTox'. It provides *in vitro* testing approach for predicting human toxicity of a compound [66].
2.	ChemIDplus	http://chem.sis.nlm.nih.gov/chemidplus/	ChemIDplus is web-based search application which allows opening structure and nomenclature authority files of chemical substances cited in National Library of Medicine (NLM) databases including the TOXNET® system.
3.	Chemical Effects in Biological Systems (CEBS)	http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm	CEBS is applying to view data in the form of biology and study design and permit data integration across studies.
4.	Terra-Base	http://www.terrabase-inc.com/	TerraTox™ databases provide for the quick search of compounds with structure/fragment-specific biological effects and properties.
5.	GENE-TOX	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX	Databank developed by the Environmental Protection Agency (EPA) through genetic toxicology.
6.	Hazardous Substances Data Bank	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB	Hazardous substance data Bank is toxicology database on National library of Medicine. It has information regarding exposure routes, industrial hygiene, emergency handling procedures, environmental fate and regulatory details.
7.	SuperToxic	http://bioinformatics.charite.de/supertoxic/index.php?site=home	Recently, this database has information of approximately 60,000 compounds which are classified according to their toxicological profiles.
8.	Aggregated Computational Toxicology Resource)	http://actor.epa.gov/actor/faces/ACToRHome.jsp	ACToR is openly access chemical toxicity database and can be used to discover potential chemical hazards to human health and the environment.
9.	Comparative Toxicogenomics Database	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CTD	CTD™-elucidates human toxicity of a compound and its molecular mechanisms by which environmental chemicals acts.
10.	Carcinogenic Potency Database	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CPDB.htm	CPD provides standardized analyses of chronic, long-term animal cancer tests and reported in the general published literature or by the National Cancer Institute and the National Toxicology Program.

Table 2: Databases containing toxicity information.

experimental or calculated data [27] (Figure 1). The toxicity of allele-chemical like pesticides can be also predicted by applying combination of methods such as 3D-QSAR, docking, Local Binding Energy (LBE) and GRID [28]. Further, OSIRIS property explorer is another in silico method for assessing the toxicity of any chemical compound. Discovery of newer drug may also bring health hazards. The information regarding toxicological profile of known toxins will make a basis to assign the toxicity of unknown compound. The Structural Bioinformatics Group, Institute of Molecular Biology and Bioinformatics, Charite (Cbf), Berlin, Germany created a SuperToxic database containing information of various toxic compounds (~60,000).

Prediction of environmental destiny of toxic compounds

Biodegradation of toxic chemicals is most important parameter influencing whether compound will be biodegraded and, if so, will the biodegradation proceed slowly or quickly. To study the biodegradability in silico there are several softwares and databases available (Table 3). Among softwares most important one is BESS (Biodegradability Evaluation and Simulation System) [29]. The prediction of biodegradation of a compound can be made possible by using BESS software based on structural description of the compound and the existing environmental condition. BESS uses promising enzymatic

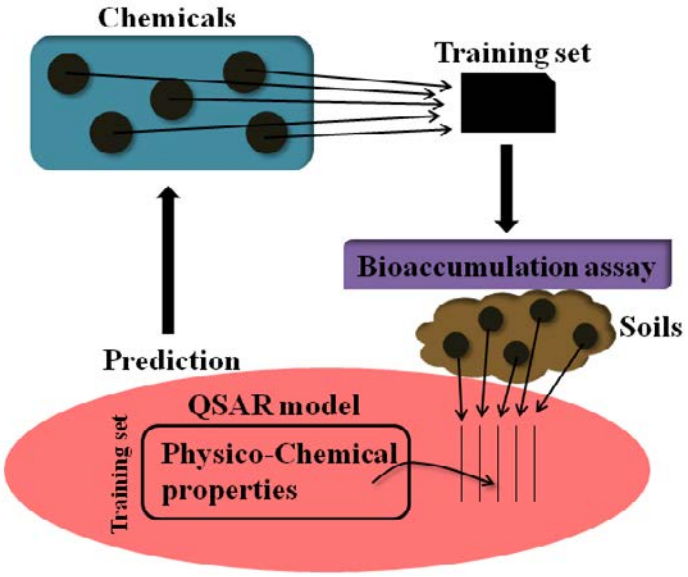

Figure 1: QSAR model for bioremediation.

S.No.	URL Code	Properties	References
1.	http://www.labmed.umn.edu/umbbd/ index.html	Prediction of biodegradation pathway	[67]
2.	http://www.labmed.umn.edu/umbbd/predictbt/	Predicting Biotransformation build on existing bio degradation information contained in the UM-BBD.	[68]
3.	http://umbbd.ahc.umn.edu/index.html	UM-BBD: University of Minnesota Biocatalysis/Biodegradation Database.	[69]
4.	http://umbbd.msi.umn.edu/predict/	UM-PPS: predicts microbial catabolic reactions using substructure searching, a rule-base and atom-to-atom mapping.	[70]
5.	http://www.genome.ad.jp/kegg/kegg2.html	KEGG: Kyoto Encyclopaedia of Genes and Genomes.	[71]
6.	http://www.expasy.org/cgi-bin/search-biochem-index	Boehringer Mannheim Biochemical Pathways on the ExPASy server, Switzerland.	[72]
7.	http://emp.mcs.anl.gov/	Enzyme and Metabolic Pathway (EMP) Database at Argonne National Laboratories.	[73]
8.	http://www.issx.org/	International society for study of Xenobiotics.	
9.	http://biocyc.org/	Biocyc: Knowledge Library of Pathway/ Genome Databases.	[74]
10.	http://www.ncgr.org/pathdb/	Path DB: Metabolic Pathways Database at NCGR.	[75]
11.	http://www.tcd.ie/Biochemistry/IUBMB-Nicholson/	Metabolic Pathway Minimaps at Trinity College, Dublin, Ireland.	[76]
12.	http://www.daylight.com/smiles/f_smiles.html	SMILES is a system for coding chemical compounds as linear strings of ASCII characters.	[77]
13.	http://biorad.igib.res.in	BioRad Base is a database for bioremediation of radioactive waste.	[78]
14.	http://bsd.cme.msu.edu	Biodegradative Strain Database	[47]
15.	http://www.epa.gov/opptintr/exposure/pubs/episuite.htm	A Windows®-based, EPI (Estimation Programs Interface) Suite™ provides physical/ chemical properties and environmental fate.	[79]

Table 3: Programme, databases and web resources containing biodegradability information.

reactions that are hierarchically organised according to knowledge of microbial physiology and ecology. Such type of prediction reduces the potential large number of enzymatic conversion which is most likely to provide anabolic intermediates or energy to micro-organisms (Figure 2a). Biochemical Network Integrated Computational explorer (BNICE) is also known for the prediction of possible microbial degradation pathways (14). It involves rules of enzyme classification system and predicts thermodynamically favoured reactions rather than using microbial physiological and ecological conditions (Figure 2b). The multi computer automated structure evaluation/ (MultiCASE/META) system combines a group-contribution model and an expert system to simulate aerobic biodegradation pathways [30]. MultiCASE approach has been also used to model anaerobic aquatic biodegradation rates [31]. Mineralization of organic compound is a significant factor when considering their fate in the environment. A model was developed and integrated into an expert software system named CATABOL which is a knowledge based expert system [32]. It can simulate the likelihood of biodegradation of organic compounds directly from their structure. However, this probabilistic model can also be useful in determining the probabilities for overall Biochemical Oxygen Demand (BOD) and extent of CO_2 production in bioremediation process [32,33]. Fate of a specific chemical spilled in a given site and even show interventions aimed at accelerating the process can be described by MetaRouter system [34]. The MetaRouter allows visualization through a web interface of all probable pathways that a large number of intractable compounds can take through known steps of all the reactions taken from the UM-BBD. The system searches in the database for all possible combination of enzymes (and wherever available, their cognate

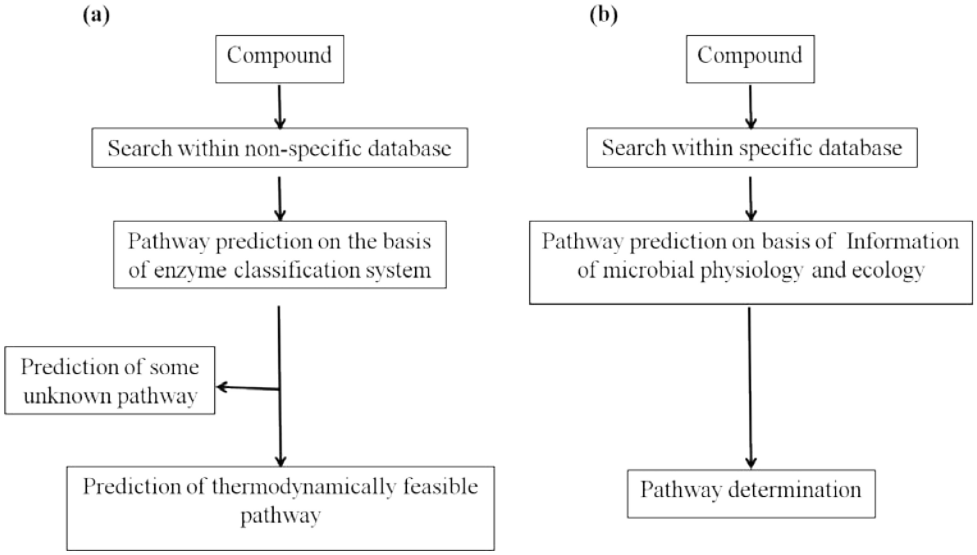

Figure 2: Comparison between pathway prediction rules between BNICE (2a) and BESS (2b).

genes) required to convert a certain substrate into their metabolic intermediates or into any other products. Through MetaRouter system a virtual pathways having meshwork of genes/enzymes can be predicted which come from different bacteria, sometimes having very different lifestyles (for instance, aerobic and anaerobic). Nevertheless, such combinations may not exist or may have not been exposed yet in nature, these cross pathways reflect probable processes that can occur at different stages and locations by divergent microorganisms. The MetaRouter system does not give information regarding kinetics or thermodynamics of the proposed pathways, although it can certainly guide metabolic engineering attempts. Although MetaRouter describes only biodegradation information for a compound and gives a picture of how given chemicals could be degraded if passed through the complex metabolism of a complex community rather than how they could be metabolized by one specialist strain [34]. Metabolic Knowledgebase (MKB) uses ontology to formalize metabolic data and apply large flexible and scalable metabolic knowledgebase to capture several levels of chemical or biological information. It develops inference tools to support complex metabolic queries to semantically integrate data from chemical structures to complete pathways; incorporate data from public domain sources. Biocatalysis Classification Scheme (BCS) uses MKB to identify subset of biocatalytic function based on pathway of interest and to find relevant compounds and infer their sub structural features. Biocatalysis Assignment Tool (BAT) uses MKB to identify relevant sets of proteins and their biocatalytic functions. It also identifies conserved features among proteins and establishes correlation between function and conserved features. Metabolic Pathway Synthesis (MPS) provides information regarding predicting enzymatic activity from the cellular environment and helps to classify pathways with respect to cellular parameters and to obtain information about metabolic pathway and its regulation. It uses BCS/MKB to find out the possible transformation from native compound to intermediates. In case of database KEGG (Kyoto Encyclopedia of Genes and Genomes), commonly used resource provides information on genes and metabolic pathways in a wide range of species [35]. KEGG consists of three databases: PATHWAY provides network of interacting molecules, GENES contains catalogs of all full and partial genome sequence and LIGAND for the collection of chemical compounds in the cell, enzyme molecules and enzymatic reactions [36].

Influence of environmental factors on biodegradation

Earlier studies of bioremediation trials were not performed under natural environmental conditions. Therefore, the impact of environmental factors on the bioremediation process was never expected. However, after the investigation of in situ bioremediation approaches now it is feasible to understand the bioremediation process is influenced significantly by environmental factors such as the physiological and chemical ambience of the contaminated environment, bioavailability of nutrients, concentration and properties of cocontaminants, level of contamination, community organization of the indigenous microbial communities [13,37-40]. Various abiotic and biotic factors play important role in bioremediation. Their dynamic interactions occur in concrete abiotic conditions which are defined by physico-chemical conditions like O_2 supply, electron transport, water, temperature, pH, salt concentration, many of which [41-43]. The above environmental factors determine the dynamic of endogenous microbial community structures along with the availability of given chemical and energy source [41].

Ecological consequences on the biodegradative strains

Knowledge of indigenous microflora is required which may or may not affect the degradation of toxic compounds by test microorganism [13]. In situ bioremediation is directly or indirectly affected by the indigenous micro flora, thus it is most important to evaluate the ecological consequences on the biodegradative strains [13,41]. There are several non related phenomenons to study these ecological consequences. However, for the development of bioremediation technology, it is required to analyze the effect on indigenous microbial community structure by the bioremediation process in a particular ecological conditions [41,42,44-46]. Biodegradative Strain Database (BSD) provides information of degradative bacteria and hazardous chemicals degraded by these bacteria [47]. It also includes corresponding literature citation, relevant patents and link to additional web based biological and chemical data. The BSD is being developed within the phylogenetic framework of the Ribosomal Database Project

II to provide a biological complement to the chemical and degradative pathway [47]. Ecological Structure Activity Relationships (ECOSAR) is a foretelling system providing information for aquatic toxicity of a compound [48]. The program estimates a chemicals acute toxicity and chronic toxicity to aquatic organisms by using computerized Structure Activity Relationships (SARs).

Discussion

As a result of worldwide extensive application of pesticides, it may get released into different environmental compartment (e.g. soil, sediment and water bodies) through waste streams and causing threat to the various life forms [3]. Thus public concern has been prompted to develop robust technology for the eradication of pesticides and restoration of environmental health. There are two ways for the decontamination of pesticides from the environment; one is nonbiological (e.g. incineration, land filling, hydrolysis, photolysis, chemical lysis and thermal decomposition) and the second is biological means [2,3,49,50]. Mostly the microbial transformation/degradation of the pesticides/ or chemical is considered as one of the most effective, ecofriendly and technologically challenging approaches for the bioremediation of toxic pollutants from the different environmental compartment [3,4,51,52]. The bioremediation database provides by University of Minnesota provides most comprehensive platform for nearly all the bioremediation pathway and helps in developing various prediction programmes using these databases [53]. Pathway prediction system (PPS) predicts possible bioremediation pathway for xenobiotics using biotransformation parameters provided by UM-BBD database as well as scientific literature [54]. Other programmes similar to PPS are METEOR, MetabolExpert, DEREK, StAR, CATABOL system, MetaRouter and MultiCASE/META [32,34,55-58]. To establish strain designation in prediction of bioremediation within phylogenetic perspective, Biodegradative Strain Database (BSD) was developed by integrating metabolic data of UM-BBD and phylogenetic data of Ribosome Database project (RPD-II) [47]. Till now dogma of the biodegradation is one strain degrades one pollutant, but information available in literature of bioremediation lack essential aspect of natural scenarios, like interchange of gene between bacteria or their metabolic network co-operation [51,59,60]. It has also been known a single microbe exhibit metabolically versatile in nature due to the presence of large size of genome and plasmid containing large number of metabolic genes, resulting in expansion of the multiple metabolic pathways [43]. However, insufficient biological information regarding the regulation of growth and metabolism in various microbial communities restricts development in the site-specific mineralization process. Similarly, the bioremediation of xenobiotic compounds either ex situ or in situ by pure isolates does not represent an actual behaviour of the microorganisms; however, it depends on cooperative metabolic activities of mixed microbial population [61-63]. Under these conditions biodegradative potential of all microbes can be crossed with the all known compounds and in silico bioremediation helps to predict the destiny of a compound whether partially or fully degraded to non toxic compounds. Bioinformatics based search will facilitate and speed up the analysis of microbial degradation of hazardous compounds. In situ bioremediation can be applied in a number of action modes including aerobic, anaerobic, anoxic (nitrate respiration) and co-metabolic. Bioinformatics have huge amount of data collected from various resources such as chemical structure and reactivity properties of compounds; protein sequence, structure and function; comparative genome analysis; phylogenetic analysis; environmental biotechnology. These informations will collectively provide a bigger picture regarding degradation of a compound in the environment (Figure 3). The above summarized computational database, software and tools and their collective integration will help to determine the environmental fate of any compounds more precisely and accurately. After predicting the more accurate the environmental fate of any compound by computational approaches, future work will be carried out to validate

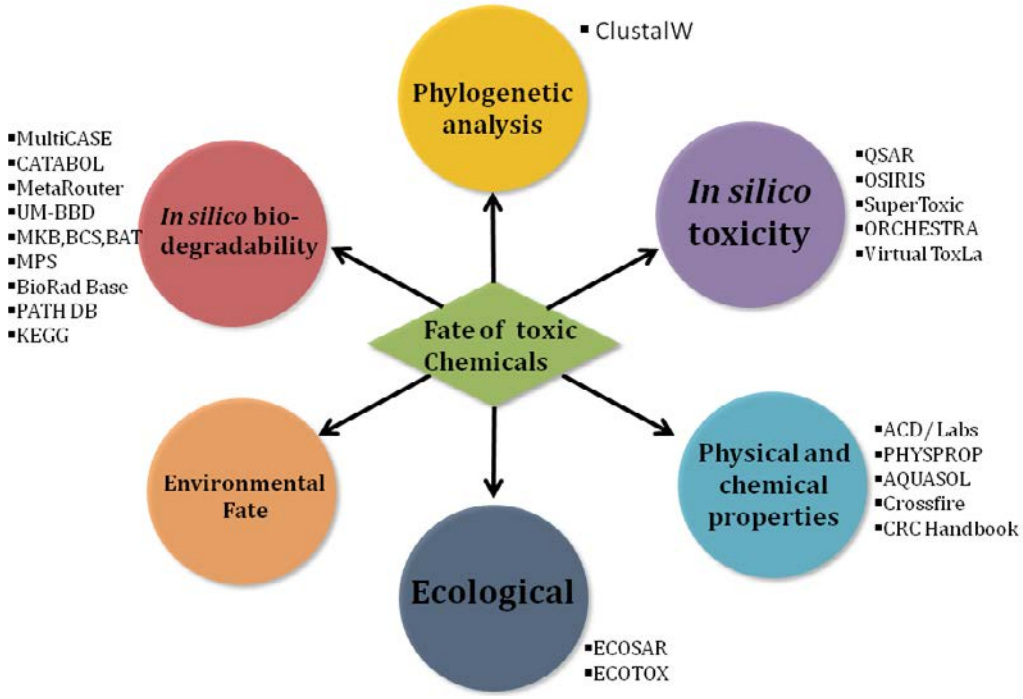

Figure 3: Schematic representations of prediction softwares and databases involve in destiny of a toxic compounds.

the complete fate of the compound by single isolate as well as by mixed microbial consortium. The pathway predicting software will also help in minimizing the number of possible combination for the development of microbial consortia.

Acknowledgements

FK thanks DBT for the Research Associate ship and MS acknowledge his research fellowship from UGC, India. This is the IMTECH communication no 0123/2013.

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